

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Li *et al.*

Group Art Unit: 1635

Serial No.: 10/574,129

Examiner: Bowman, Amy Hudson

Filed: November 2, 2006

Docket No.: 180/179 PCT/US

Confirmation No.: 9249

For: A NOVEL siRNA-BASED APPROACH TO TARGET THE HIF- $\alpha$  FACTOR FOR  
GENE THERAPY

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DECLARATION OF CHUAN LI, PH.D. PURSUANT TO 37 C.F.R. §1.132

Commissioner for Patents  
P. O. Box 1450  
Alexandria, VA 22313-1450

Sir:

1. My name is Chuan Li, Ph.D., and I am Director of Molecular Radiation Oncology at the University of Colorado at Denver's School of Medicine.
2. A true and accurate copy of my *curriculum vitae*, which evidences my expertise and credentials, is attached herewith and labeled **Exhibit B**.
3. I am a co-inventor of the above captioned U.S. Patent Application Serial No. 10/574,129.
4. I have had an opportunity to review pending claims 36, 38-42, 45-59, 62, and 63 in the above captioned U.S. Patent Application Serial No. 10/574,129.

5. I have also had the opportunity to review the Non-Final Official Action dated December 18, 2008 (hereinafter the "Non-Final Official Action") from the United States Patent and Trademark Office (hereinafter "the Patent Office").

6. Various siRNAs were tested for their abilities to downregulate HIF-1 $\alpha$  activity by producing retroviruses that encode various siRNAs that target the human HIF-1 $\alpha$  mRNA sequence. Retroviruses encoding siRNA sequences targeted to the various sequences in the human HIF-1 $\alpha$  gene were produced that targeted the following human HIF-1 $\alpha$  nucleotide sequences:

ATGACATGAAAGCACAGAT (siRNA 1);

AACTGGACACAGTGTGTTT (siRNA 2);

AAATGAGAGAAATGCTTAC (siRNA 3); and

AAATGGCCTTGTGAAAAAG (siRNA 4).

7. siRNA 1 included a sense sequence that corresponded to SEQ ID NO: 7 of the above captioned U.S. Patent Application Serial No. 10/574,129. The other three siRNAs were targeted to sequences in the vicinity of the sequence targeted by siRNA 1 as shown in **Exhibit C** submitted herewith.

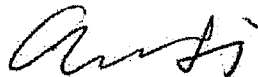
8. The retroviruses were used to infect the human colon cancer cell line HCT116. After infection, the cells were treated with puromycin, which selected for stable integration of the retrovirus genomes. After 5 day of selection, puromycin was washed off the cells, and the cells were subjected to hypoxia (0.5% O<sub>2</sub>) treatment for 24 hours. After 24 hours treatment, the cells were lysed and assayed for HIF-1 activity using a commercially available kit purchased from Active Motif of Carlsbad, California.

9. The results of these assays are presented in **Exhibit D** submitted herewith. Normoxic cells containing each of the siRNAs were used as controls for normalization. Control indicated vector infected control cells.

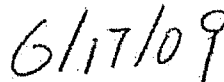
10. As can be seen in **Exhibit D**, the retrovirus that encoded an siRNA that included SEQ ID NO: 7 (*i.e.*, siRNA 1) showed superior ability to downregulate HIF-1 activity as compared to any of siRNAs 2-4. Specifically, cells containing siRNAs 2, 3, and 4 showed about 50-300% higher HIF-1 activity levels than cells containing siRNA 1.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,



Chuan Li, Ph.D.



Date

Attachments: **Exhibits B-D**

## Exhibit B

### Curriculum Vitae

## Chuan-Yuan Li

### Personal Information

**Tel:** (303) 724-1542

**Fax:** (303) 724-1554

**Email:** Chuan.Li@ucdenver.edu

### ***Citizenship:***

U.S. Citizen.

### Education

**B.S. in Chemistry**, 1987, University of Science & Technology, Hefei, China.

**Ph.D. in Cancer Biology**, 1993, Harvard University, Cambridge, MA.

### Professional Experience

- 2006- Professor of Pharmacology, University of Colorado Health Sciences Center, Aurora, CO.
- 2006- Professor and Director, Division of Radiation and Cancer Biology, Dept. of Radiation Oncology, University of Colorado Health Sciences Center, Denver, CO.
- 2005-2006 Professor, Departments of Radiation Oncology, Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC
- 2002-2005 Associate Professor, Dept. of Radiation Oncology, Duke University Medical Center, Durham, NC
- 1997-2002 Assistant Professor, Dept. of Radiation Oncology, Duke University Medical Center, Durham, NC
- 1993-1996 Postdoctoral research fellow, Harvard University, Boston, MA

### Honors and Awards

- 1987-89 Rohm and Haas Fellowship for graduate study at Harvard University
- 1990 Student Travel Award, 39th Radiation Research Society Annual Meeting, New Orleans, LA
- 1991 Student Travel Award, 9th International Congress of Radiation Research, Toronto, CA
- 1993 Kresge Center for Environmental Science pilot grant, Harvard University
- 1999 Komen Foundation Grant for Breast Cancer Research
- 2001 Best Poster Award, Annual Meeting of the Duke University Cancer Center
- 2002 Best Proffered Paper, 6<sup>th</sup> Wolfsberg Symposium in Radiation Oncology, Ematingen, Switzerland, 2002
- 2006 Michael Fry Research Award from the Radiation Research Society, Philadelphia, PA.

### Awards obtained by graduate students and postdoctoral fellows.

- 2005 AACR Travel Award, Fang Li, Postdoc Anaheim, CA
- 2005 RRS travel Award, Postdoc Fang Li
- 2005 RRS travel award, Postdoc Shanling Liu
- 2005 Excellence and Soundness of Research Methods award from the Fifth International Symposium on Therapeutic Ultrasound, Student: Yunbo Liu

## Exhibit B

### Curriculum Vitae

- 2006           Scholarship to attend the Keystone symposium in Hypoxia research for Fang Li, postdoc.  
2006           Scholarship to attend AACR special conference on genetic susceptibility to cancer, Bin Yan.  
2008           Travel Award for postdoc Wenrong Li to attend 54<sup>th</sup> annual meeting of RRS.

### **Membership in Professional Societies**

Radiation Research Society, Member of the Educational Committee  
American Association for Cancer Research  
American Society of Gene Therapy  
International Society of Stem Cell Research

### **Reviewership**

#### ***Reviewers for Academic Journals:***

Molecular Cell, Cancer Research, Clinic Cancer Research, Gene Therapy, J. of National Cancer Institute, Molecular Therapy, International J. of Cancer, J. of Investigative Dermatology, Int. J. of Hyperthermia, Int. J. of Radiation Oncology, Biology and Physics, Leukemia, etc.

#### ***Grant Review Committee Membership:***

*Ad hoc* member, NIH study section of Metabolic Pathology, 2001-2003. Radiation Therapeutics and Biology (RTB), 2003-2004, 2007-present;  
Komen Foundation for Breast Cancer Research, 2000  
NASA Fundamental Space Biology Research Program, 2004, 2005  
DOE Low Dose Radiation Research Program, 2004  
Clinical and Basic Science Grant Review Panel, National Science Foundation of China, 2005-Present.

### **Invited Presentation(selected)**

1. Elevated frequency of microsatellite mutations in human lymphocyte cells selected for mutation a at the thymidine kinase locus, *41st Annual Meeting of the Radiation Research Society*, Dallas, Texas, 1993.
2. Involvement of tumor suppressor genes in human cell transformation, *Workshop on Neoplastic transformation in human cell systems in culture: Mechanisms of Carcinogenesis*, Chicago, Illinois, 1995.
3. A Heat-Induced Gene Therapy Approach for Cancer Treatment, *46th Annual Meeting of the Radiation Research Society*, Dallas, Texas, 1998.
4. Hyperthermia-regulated gene therapy. Annual meeting of the North America Hyperthermia Society, Philadelphia, PA, 1999
5. Combined radiation and gene therapy treatment of breast cancer in murine tumor models, *Annual Research Meeting of the Komen Foundation for Breast Cancer Research*, Washington DC, 2000
6. Progress in hyperthermia-regulated gene therapy (Keynote Address), *The 17<sup>th</sup> Annual Meeting of the Japanese Society of Hyperthermic Oncology*, Niigata, Japan, 2000
7. Heat-controlled genet therapy, *International Conference of Stress Proteins in Biology and Medicine*, Woods Hole, MA, 2000
8. Persistent genetic instability in cancer cells induced by non-DNA damaging stress, *Gordon Conference on Radiation Oncology*, Ventura City, CA, 2001

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### Curriculum Vitae

9. Heat-induced transcriptional Targeting of therapeutic genes to cancer, 48<sup>th</sup> annual Meeting of the Radiation Research Society, Puerto Rico, 2001
10. Increased resistance of cancer cells mediated by the ILK gene, 49<sup>th</sup> annual meeting of the Radiation Research Society, Reno, NE, 2002
11. Tumor therapy by use of adenovirus vectors that target tumor cells genetically, 6<sup>th</sup> Wolfsberg Symposium in Radiation Oncology, Ematingen, Switzerland, 2002.
12. Telomerase-targeted oncolytic virus gene therapy, Annual Meeting of the North American Hyperthermia Society, Quebec City, Quebec, Canada, 2003.
13. Targeted gene therapy for cancer, 10<sup>th</sup> SCBA International Symposium, Beijing, China, 2004.
14. Minisymposium presentation, AACR annual meeting, Anaheim, CA, 2005.
15. Invited presentation, NIH conference on Bioimaging, DC, 2005
16. Invited presentation, Radiation Research Society, Denver, Colorado, 2005.
17. Invited Speaker, Division of Pharmaceutical Sciences, University of Wisconsin, Madison, 2006
18. Invited Speaker, Ontario Cancer Institute, Toronto, Canada, 2006

### **Teaching Activities**

**Cancer Biology** (1997-1999), offered by DUMC Cancer Center, Primary Instructor: Dr. EC Halperin.

**Radiation Biology**(1997-2006), offered by Dept. of Radiation Oncology, DUMC; Primary Instructor: Chuan-Yuan Li.

**Biomedical Engineering 260** (1997-2005), offered by Dept. of Biomedical Engineering, Duke University School of Engineering. Primary Instructor: Dr. F. Yuan.

**Biology of Radiation Therapy**, offered by Dept of Radiation Oncology, University of Colorado Denver School of Medicine. Primary Instructor: Chuan-Yuan Li.

### **Grant Support**

#### **Past Support**

Development of a novel gene therapy approach based on hyperthermia. Duke Breast SPORE pilot project. Amount: \$18,000; Duration: 07/97-06/98. PI; Chuan-Yuan Li

Development of Biological Sensor for Stress exposure. Pilot project funded by the Duke University Marine Biology Center. Amount \$15,000. Duration 07/98-06/99. PI: Chuan-Yuan Li

Hyperthermia-controlled gene therapy, Celsion Cooperation. Amount: \$50,000; Duration 1998-1999. PI: Chuan-Yuan Li

A hyperthermia-mediated gene therapy approach for cancer. NIH 1R01CA81512. Amount: \$120,000/yr direct cost. Duration: 1998-2003. PI: Chuan-Yuan Li

Isolation and Characterization of Angiogenesis-related genes in the tumor vasculature. Glaxo-Wellcome-Duke Collaborative Research Agreement. Amount: \$300,000. 1999-2001. PI: Chuan-Yuan Li

Enhancement of breast cancer radiotherapy by genetic immunotherapy. Komen Foundation for Breast Cancer Research. Amount: \$250,000. Duration: 1999-2001. PI; Chuan-Yuan Li

## Exhibit B

### Curriculum Vitae

A Replication-competent Adenovirus That Targets Hypoxic Tumor Cells. Duke Comprehensive Cancer Center. Discovery Research Group Grant. Amount: \$30,000. Duration: 2002. PI: Chuan-Yuan Li.

A novel transgenic mouse model for studying tumor hypoxia and angiogenesis. Morris Cancer Foundation & NIH imaging Pilot grant. Amount: \$100,000. Duration: 2002-03. PI: Chuan-Yuan Li.

Hyperthermia and perfusion effects in cancer therapy. NIH 5PO1 CA42745. Amount \$17,000,000. Duration: 2000-2005. PI: M.W. Dewhirst. 10% effort for C-Y. LI

SPORE in Breast Cancer. NIH 5P50-CA-68438. Amount: \$1,851,120. Duration: 2002-2007. PI: Lyerly. 15% Effort for C-Y. Li

Enhancement of Prostate Cancer Radotherapy by immunogene therapy. Department of Defense. Amount: \$215,000. Duration: 2002-2006. PI: Chuan-Yuan Li

Mechanistic studies of tumor therapy by electrofusion. NIH. Amount: 200K/yr annual direct cost. Duration: 2002-2007. PI: F. Yuan. 10% effort for C-Y. Li.

A novel adenovirus vector that targets telomerase-expressing breast cancer cells. Komen Foundation for Breast Cancer Research. Amount: \$250,000/3yrs. Duration: 2003-2007. PI: Chuan-Yuan Li

Molecular Dissection of the roles of SOD genes in mammalian cellular response to low dose radiation. DOE. Amount: \$900K for 3 years. 2003-2007. PI: C-Y. Li

Ultrasound-mediated gene delivery and activation. NIH. Amount \$1,250,000. Duration: 2003-2008. PI: Pei Zhong. 10% effort for C-Y. Li.

A hyperthermia-mediated gene therapy approach for cancer. NIH 1R01CA81512. Amount: \$150,000/yr direct cost. Duration: 2003-2009. PI: Chuan-Yuan Li

HZE particle induced persistent genetic instability/oncogenic transformation and their prevention. National Aeronautics and Space Administration (NASA). Amount: 200K/yrs. Duration: 2003-2008. PI: C-Y. Li

Imaging tumor hypoxia in a transgenic mouse model. NIH R21 EB001882. Amount: \$500,000 total. Duration: 2003-2007. PI: Chuan-Yuan Li

### *Active/Current Support*

University of Colorado SPORE in Lung Cancer (NCI). PI: Paul Bunn. Amount: \$2,500,000/yr. Duration: 2008-2013. Part for C-Y. Li, Developmental Project: \$50,000/yr direct cost.

## Exhibit B

### Curriculum Vitae

Roles of HIF-1 genes in head and neck cancer radiotherapy (NIH/NCI). PI: Chuan-Yuan Li, Duration: 01/01/2009-12/31/2013. Amount: \$200K/yr direct, \$300K/yr total.

Mechanistic studies of space radiation induced carcinogenesis (NASA). PI: Chuan-Yuan Li, Duration: 06/01/2009-05/31/2010. Amount: \$220K/yr direct, \$354K/year total.

Mechanistic studies of tumor response to cytotoxic chemotherapy (NIH/NCI). Duration: 07/01/2009-06/30/2014; PI: Chuan-Yuan Li; Amount: 200K/yr direct, \$300K/yr total.

### **Publications**

#### ***Peer-Reviewed Publications:***

1. Li, C-Y., Yandell, D.W., and Little, J.B. Molecular Mechanisms of Spontaneous and Induced Loss of Heterozygosity in Human Cells In Vitro (1992). *Somatic Cell and Molecular Genetics*, Vol. 18, 77-87.
2. Li, C-Y., Yandell, D.W., and Little, J.B. Evidence for Coincident Mutations in Human Lymphoblast Clones Selected for Functional Loss of a Thymidine Kinase Gene(1992). *Molecular Carcinogenesis*, Vol. 5, 270-277.
3. Spiro, I. J., Yandell, D.W., Li, C-Y. , Saini, S., Ferry, J., Powelson J., Katkov, W.N., and Cosimi, A.B. Lymphoma of Donor Origin Occuring at the Porta Hepatis of Transplanted Liver(1993). *New England Journal of Medicine*, Vol.329, 27-29.
4. Poremba, C., Dockhorn-Dworniczak, B., Merrit, V., Li, C-Y., Heidle, G., Tauber, P., Bocker, W., , and Yandell, D.W. Immature Teratomas of Different Origin Carried by a Pregnant Mother and Her Fetus(1993). *Diagnostic Molecular Pathology* , Vol.2, 131-136.
5. Li, C-Y., Yandell, D.W., and Little, J.B. Elevated frequency of Microsatellite Mutations in Human Lymphoblast Clones Selected for Mutations at Thymidine Kinase locus(1994). *Molecular & Cellular Biology* , Vol. 14, 4373-4379.
6. Li, C-Y., Nagasawa, H., and Little, J.B. Confluent Holding Recovery in Irradiated Human Diploid Fibroblasts: Possible Role of the p53/Waf1 Signal Transduction Pathway(1995). *Journal of Cellular Biochemistry*, (S) 21A, 340.
7. Li, C-Y., Nagasawa, H., Tsang, N., and Little, J.B. Radiation-Induced Irreversible G0/G1 Block is Abolished in Human Diploid Fibroblasts Transfected with the Human Papilloma Virus E6 gene: Implication of the p53-Cip1/WAF1 pathway (1995). *International Journal of Oncology*, Vol. 223-236.
8. Li, C-Y., Suardet, L., and Little, J.B. Potential Role of WAF1/Cip1/p21 as a Mediator of TGF-b Cytoinhibitory Effect . *Journal of Biological Chemistry*, Vol. 270 No. 10., 1995 pp4971-4974.



## Exhibit B

### Curriculum Vitae

9. Nagasawa, H., **Li, C-Y.**, Maki, C.G. , Imrich A. and Little, J.B. Relationship between Radiation-Induced G1 Phase Arrest and p53 Function in Human Tumor Cells. *Cancer Research* vol 55 No. 9, 1995, pp1842-1846.
10. Little, J.B. , Nagasawa, H., Keng, P., and **Li, C-Y.** Absence of Radiation-induced G1-arrest in Two Closely Related Human Lymphoblast Cell Lines That Differ in p53 Status *Journal of Biological Chemistry* Vol.270, No. 19, 1995 pp11033-11036.
11. Tsang, N., Nagasawa, H., **Li, C-Y.**, and Little, J.B. Abrogation of p53 function by Transfection of HPV16 E6 Gene Enhances the Resistance of Human Diploid Fibroblasts to Ionizing Radiation *Oncogene* vol. 10, 1995, pp2403-2408.
12. **Li, C-Y.**, Nagasawa, H., Dahlberg, W.A., and Little, J.B. Diminished Capacity for p53 in Mediating a Radiation-Induced G1 Arrest in Established Human Tumor Cell Lines *Oncogene* vol. 9, No. 9, 1995, pp1885-1892.
13. Little, J.B., **Li, C-Y.**, Nagasawa, H., Pfenning, T., and Vetrovs, H. Genomic Instability and Radiation Mutagenesis(1996) *J. Chimie Phys.* vol. 93, 157-164.
14. **Li, C-Y.**, Nagasawa, H., Dahlberg, W.A., and Little, J.B. The Role of Tumor Suppressor Genes in Determining a Radiation-induced G1-arrest and Human Cell Carcinogenesis(1996) *Radiation Oncology Investigations*, vol. 3, 268-271.
15. Huang, H-M., **Li, C-Y.**, Little, J.B. Abrogation of p53 Function in Human Tumor Cells Does Not Alter Their Sensitivity to Ionizing Radiation(1996). *International Journal of Radiation Biology*, vol. 70 (2), 151-160.
16. Suardet, L., **Li, C-Y.**, and Little J.B. Radio-induced modulation of transforming growth factor sensitivity in a p53 wild-type human colorectal cancer cell line(1996). *International Journal of Cancer* vol. 68(1), 126-31.
17. Huang, Q., Tao., Y., **Li, C-Y.**, and Yandell, D. The status of p16 and p15 in primary tumors and cell lines (1996). *Chinese Journal of Medical Genetics*, vol. 13, 198-202.
18. Yu, Y., **Li, C-Y.**, Little, J.B. Abrogation of p53 function by HPV16 E6 gene delays apoptosis and enhances mutagenesis but does not alter radiosensitivity in TK6 human lymphoblastoid cells(1997). *Oncogene*, vol. 14(14), 1661-1667.
19. Little JB, **Li C-Y.**, Nagasawa H, Huang H. Influence of p53 expression on radiosensitivity of human normal and tumor cells(1998). *J CHIM PHYS* vol 95,820-829.
20. Tao, Y., Huang, Q., **Li, C-Y.**, and Yandell, D. Deletions and point mutations of p16, p15 gene in primary tumors and tumor cell lines. (1999). *Chinese Med Sci. J.* vol.14, 200-235.
21. Huang, Q., Shan, S, Braun, R.D., Lanzen, J., Anyrhambatla, G., Kong, G., Borelli, M., Corry, P., Dewhirst, M.W., and **Li, C-Y.** GFP based non-invasive, in vivo monitoring of gene expression(1999). *Nature Biotechnology*, vol 17, 1033-1035.

## Exhibit B

### Curriculum Vitae

22. Li, C-Y., Huang, Q., Braun, R.D., Lanzen, J., Hu, K., Lin, P., Dewhirst, M.W. Initial stages of tumor cells-induced angiogenesis:evaluation via skin window chambers in rodent models(2000) *Journal of the National Cancer Institute*, vol 92, 143-127.
23. Huang, Q., Li, C-Y. Comparative studies of GFP gene transgene by viral and non-viral approaches (2002). *Chinese J. Pathology*. Vol 29, 143-144.
24. Huang, Q., Li, C-Y. Dynamic observation of tumor cell growth by use of GFP-transduced tumor cells (2000). *Chinese J. Pathology*. Vol 29, 230-232.
25. Huang, Q., Xu, P., Liu, WW., Wang, F., Gu, Q., Tian, SH., Fan, Y., Xie, KC., Chen, XF., Li, C-Y. Preparation of green fluorescent protein retrovirus and its application in mediating gene transfer into retinal pigment epithelial cells (2001). *Chinese J. of Ophthalmology*, vol. 37, 248-251.
26. Li, C-Y., Huang, Q., Braun, R.D., Lanzen, J., Hu, K., Lin, P., Dewhirst, M.W. Re: Initial stages of tumor cell-induced angiogenesis: Evaluation via skin window chambers in rodent models - Response(2000). *Journal of the National Cancer Institute*, Vol. 92, 1445-1446.
27. Huang,Q., Hu, K., Lohr, F., Zhang,L., Braun, R., Lanzen,J., Little,JB., Dewhirst,MW., and Li, C-YHeat-induced Gene Expression as a Novel Targeted Cancer Gene Therapy Strategy.(2000) *Cancer Research*, vol. 60, 3435-3439.
28. Lohr, F., Hu, K., Huang, Q., Zhang, Li., Dewhirst, MW., and Li, C-Y. Enhancement of Radiotherapy by Hyperthermia-regulated Gene Therapy.(2000). *International Journal of Radiation Oncology, Biology and Physics*. Vol.48, 1513-1518.
29. Lohr,F., Hu, K., Haroon,Z., Samulski, TV., Huang,Q., Beaty,J., Dewhirst,MW., and Li, C-Y. Combination treatment of murine tumors by adenovirus mediated local B7/IL12 immunotherapy and radiotherapy(2000). *Molecular Therapy*, vol2, 195-203.
30. Li, C-Y., Shan, S., Cao, Y., Dewhirst, M.W. Role of incipient angiogenesis in cancer metastasis.(2000). *Cancer Metastasis Reviews*, vol 19, 7-11.
31. Li, C-Y., Little, JB. Hu, K., Zhang, W., Zhang, L., Dewhirst, MW., Huang, Q. Persistent genetic instability in cancer cels induced by non-DNA damaging stress exposures (2001). *Cancer Research* vol 60, 428-432
32. Zhang, X., and Li, C-Y. Generation of recombinant adeno-associated virus vectors by a complete adenovirus-mediated approach(2001). *Molecular Therapy* vol.3, 787-792.
33. Xie, KC., Xu, P., Gu, Q., Liu, WW., Wang, F., Tian SH., Chen, XF., Li, C-Y., Huang, Q. Using GFP retrovirus to label tumor cells and vascular endothelial cells. *Chinese J. Lung Cancer*. Vol 4, 20-24.
34. Lohr,F., Lo, D., Zaharoff, DA., Hu, K., Li, Y., Zhang, X., Dewhirst, MW., Yuan, F., and Li, C-Y. Effective tumor therapy with plasmid-encoded IL12 and IL2 combined with in vivo electroporation (2001) *Cancer Research* vol 61, 3282-3285

## Exhibit B

### Curriculum Vitae

35. Huang, Q., and Li, C-Y. Using hsp70 promoter to regulate target gene expression in tumor. *Chinese J. of Pathology.*, vol. 30, 198-201.
36. Lohr, F., Huang, Q., Hu, K., Dewhirst, MW., and Li, C-Y. An inducible method for preventing systematic effects of toxic therapeutic genes delivered by intratumorally injected adenovirus vectors. *Clinical Cancer Research.* Vol. 11, 3625-3628
37. Zhang, X., Hu, K., and Li, C-Y. Protection against oxidized LDL-induced vascular endothelial cell death by integrin-linked kinase (2001). *Circulation* vol 104, 2762-2766.
38. Zaharoff, D., Barr, R., Li, C-Y., Yuan, F. Mechanistic studies of electric pulse mediated gene transfer in murine tumors (2002). *Gene Therapy.* Vol. 9, 1286-1290.
39. Wang, F., Chen, X., Tian, Y., Wu, J., Li, L., Li, C-Y., Huang, Q. Target gene transfer mediated by electroporation for cancer therapy in vivo (2002). *Progress in Biochemistry and Biophysics.* Vol. 29, 734-740.
40. Li, C-Y., and Dewhirst, M.W. Hyperthermia-regulated immunogene therapy (2002). *International Journal of Hyperthermia* Vol. 18, 589-96.
41. Dewhirst, M.W., Cao, Y., Moeller, B., Li, C-Y. Intravital Fluorescence facilitates the measurement of multiple physiological parameters and gene expression in tumors of living animals. *Disease Markers.* 18 (5-6): 293-311 2002
42. Azzam, EI, Nagasawa, N., Yu, Y., Li, C-Y. and Little, JB. Cell Cycle Deregulation and XPC Cell Transformation (2002). *Journals of Investigative Dermatology.* Vol 119, 1350-1354.
43. Baker-LePain, J.C., Sarzotti-Kelsoe, M., Fields, T.A., Li, C-Y., Nicchita, C.V. GRP94(gp96) and GRP94 N-Terminal binding domain elicit tissue non-restricted tumor suppression.(2002) *Journal of Experimental Medicine* Vol. 196, 1447-59.
44. Wang, F., Tian, Y., Li, L., Chen, X., Hu, HH. Li, C-Y., Huang, Q. Inhibition of tumor angiogenesis, growth, and metastasis by blocking VEGF paracrine pathway (2002). *Acta Biochimica et Biophysica Sinica,* vol 34.,165-170.
45. Zhang, X., Li, Y., Yan, B., Huang, Q., Dewhirst, M.W., Li, C-Y. Increased resistance of tumor cells to hyperthermia mediated by integrin-linked kinase (2003). *Clinical Cancer Research* Vol 9, 1155-60.
46. Wang, Y., Hu, JK., Krol, A., Li, Y-P., Li, C-Y., Yuan, F. Systemic dissemination of viral vectors during intratumoral injection.(2003). *Molecular Cancer Therapeutics.* Vol. 1233-1241.
47. Wang, F., Wu, J., Tian, Y., Chen, X., Hu, H., Wu, W., Li, C-Y., and Huang, Q. Role of VEGF in the growth and metastasis of a murine bladder carcinoma. (2003) *Chinese Science Bulletin.* Vol 48:2404-2410.

## Exhibit B

### Curriculum Vitae

48. Huang, Q., Wang, H., Zhang, XW., Yan, B., Dewhirst, MW., and Li, C-Y. A conditionally replicative adenovirus targeted to telomerase-positive cancer cells. (2004)*Clinical Cancer Research*. Vol: 4:1439-1445
49. Shan, S., Robson, N. D., Cao, Y., Qiao, T., Li, C. Y., Kontos, C. D., Garcia-Blanco, M., Dewhirst, M. W. Responses of vascular endothelial cells to angiogenic signaling are important for tumor cell survival.(2004) *Faseb Journal*. Vol : 17(15)\_published online.
50. Zhang, X., Huang, Q., Li, Y., Yang, H., and Li, C-Y. GW112, a novel gene involved in the survival of cancer cells under stressful conditions. (2004)*Cancer Research*. Vol. 64: 2474-2481.
51. Moeller, B. J.; Cao, Y., Li, C. Y., Dewhirst, M. W. Radiation activates HIF-1 to regulate vascular radiosensitivity in tumors; Role of reoxygenation, free radicals, and stress granules (2004) *Cancer Cell*. Vol 5: 429-441.
52. Moeller, B.J., Cao, Y., Vujaskovic, Z., Li, C.Y., Haroon, Z.A., Dewhirst, M. W.(2004) The relationship between hypoxia and angiogenesis. *Seminars in Radiation Oncology*. Vol 14:215-21.
53. Herskind C, Fleckenstein K, Lohr J, Li CY, Wenz F, Lohr F (2004) Antitumoral action of interferons and interleukins in combination with radiotherapy. Part 1: Immunologic basis. *STRAHLENTHERAPIE UND ONKOLOGIE* 180 (4): 187-193
54. Herskind C, Fleckenstein K, Lohr J, Li CY, Frederik W, Lohr F. (2004) Antitumoral action of Interferons and interleukins in combination with radiotherapy. part II: Radiobiological and immunologic strategies. *STRAHLENTHERAPIE UND ONKOLOGIE* 180 (6): 331-339
55. Zhang,X., Wang, H., Kon, T., Huang, Q., Dewhirst, MW., and Li, C-Y. Enhancement of tumor cell death in vitro and radiation therapy in vivo by use of an siRNA targeted to HIF1- $\alpha$  (2004). *Cancer Research*. Vol 64:8139-42.
56. V. Rao, P. Deng, R. Maddala, D. Epstein, C-Y. Li, Hiroaki Shimokawa (2005) Expression of dominant negative Rho-binding domain of Rho-kinase in organ cultured human eye anterior segments increases aqueous humor outflow. *Molecular Vision*, Vol 11: 288-97.
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## Exhibit C

### SEQ ID NO: 1 - Human HIF-1 $\alpha$ Coding Sequence

atg	gag	ggc	gcc	ggc	ggc	gcg	aac	gac	aag	aaa	aag	ata	agt	tct	gaa	5	10	15
Met	Glu	Gly	Ala	Gly	Gly	Ala	Asn	Asp	Lys	Lys	Lys	Ile	Ser	Ser	Glu			
cgt	cga	aaa	gaa	aag	tct	cga	gat	gca	gcc	aga	tct	cgg	cga	agt	aaa	20	25	30
Arg	Arg	Lys	Glu	Lys	Ser	Arg	Asp	Ala	Ala	Arg	Ser	Arg	Arg	Ser	Lys			
gaa	tct	gaa	ggt	ttt	tat	gag	ctt	gct	cat	cag	ttg	cca	ctt	cca	cat	35	40	45
Glu	Ser	Glu	Val	Phe	Tyr	Glu	Leu	Ala	His	Gln	Leu	Pro	Leu	Pro	His			
aat	gtg	agt	tcg	cat	ctt	gat	aag	gcc	tct	gtg	atg	agg	ctt	acc	atc	50	55	60
Asn	Val	Ser	Ser	His	Leu	Asp	Lys	Ala	Ser	Val	Met	Arg	Leu	Thr	Ile			
agc	tat	ttg	cgt	gtg	agg	aaa	ctt	ctg	gat	gct	ggg	gat	ttg	gat	att	65	70	75
Ser	Tyr	Leu	Arg	Val	Arg	Lys	Leu	Leu	Asp	Ala	Gly	Asp	Leu	Asp	Ile			80

### SEQ ID NO: 7 (siRNA 1)

gaa	<b>gAT GAC ATG AAA GCA CAG ATg</b>	aat	tgc	ttt	tat	ttg	aaa	gcc	ttg	85	90	95						
Glu	Asp Asp Met Lys Ala Gln Met Asn Cys Phe Tyr Leu Lys Ala Leu																	
gat	ggt	ttt	ggt	atg	ggt	ctc	aca	gat	gat	ggt	gac	atg	att	tac	att	100	105	110
Asp	Gly	Phe	Val	Met	Val	Leu	Thr	Asp	Asp	Gly	Asp	Met	Ile	Tyr	Ile			
tct	gat	aat	gtg	aac	aaa	tac	atg	gga	tta	act	cag	ttt	gaa	cta	<b>act</b>	115	120	125
Ser	Asp	Asn	Val	Asn	Lys	Tyr	Met	Gly	Leu	Thr	Gln	Phe	Glu	Leu	Thr			

### siRNA 2

<b>gga cac agt gtg ttt</b>	gat	ttt	act	cat	cca	tgt	gac	cat	gag	<b>gaa atg</b>
Gly His Ser Val Phe Asp Phe Thr His Pro Cys Asp His Glu Glu Met										
130	135	140								

### siRNA 3

<b>aga gaa atg ctt aca</b>	cac	aga	<b>aat ggc ctt gtg aaa aag</b>	ggg	aaa	gaa
Arg Glu Met Leu Thr His Arg Asn Gly Leu Val Lys Lys Gly Lys Glu						
145	150	155				160

### siRNA 4

caa	aac	aca	cag	cga	agc	ttt	ttt	ctc	aga	atg	aag	tgt	acc	cta	act	165	170	175
Gln	Asn	Thr	Gln	Arg	Ser	Phe	Phe	Leu	Arg	Met	Lys	Cys	Thr	Leu	Thr			



Exhibit D

